Neuromuscular

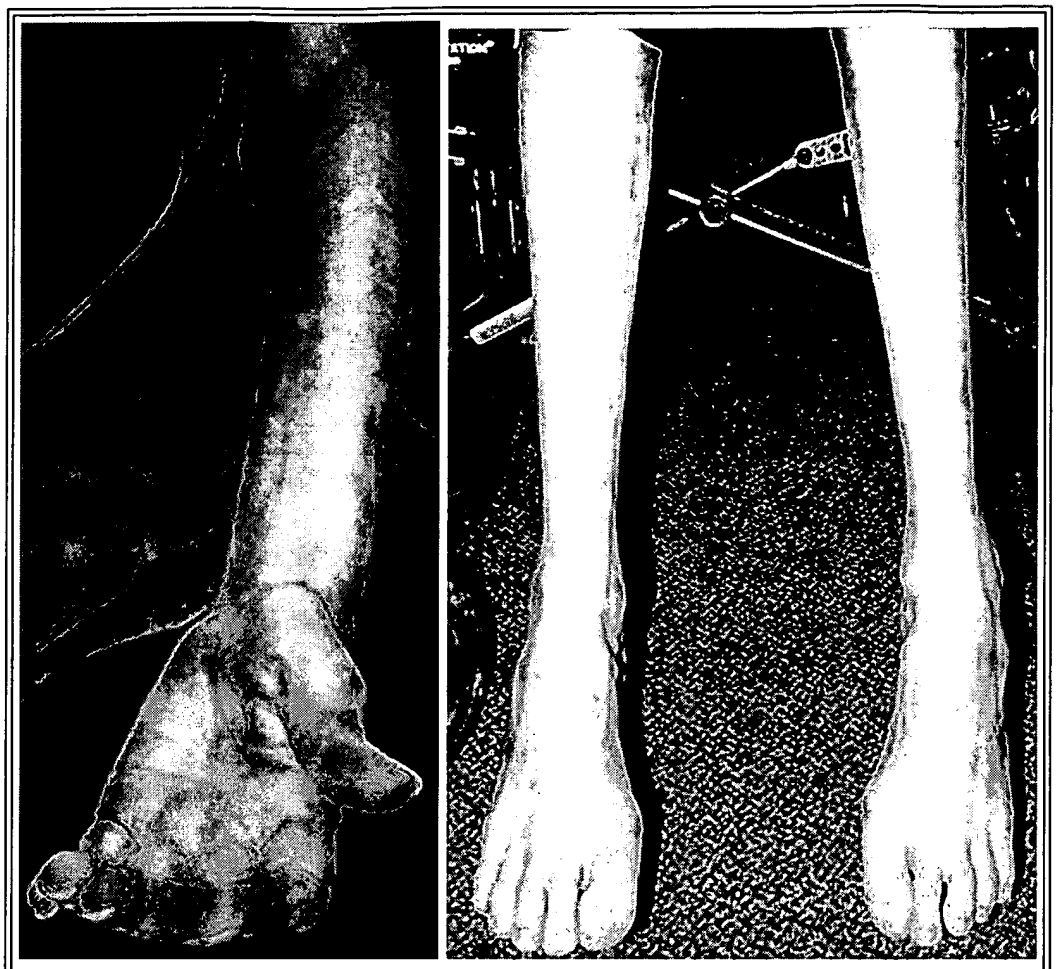
WASTING > WEAKNESS

- Pathology is often Type II muscle fiber atrophy.
  - Cachexia (weight loss > 15%)
  - Aging
  - Disuse
  - Endocrine myopathies: Corticosteroid excess; Hyperthyroidism
  - Paraneoplastic Neuromyopathy
- Other disorders with prominent **wasting associated** with weakness
  - Congenital myopathies
  - Congenital myasthenic syndromes
  - Denervation
  - HIV **wasting**

METABOLIC CHANGES IN SYSTEMIC DISORDERS WITH MUSCLE WASTING

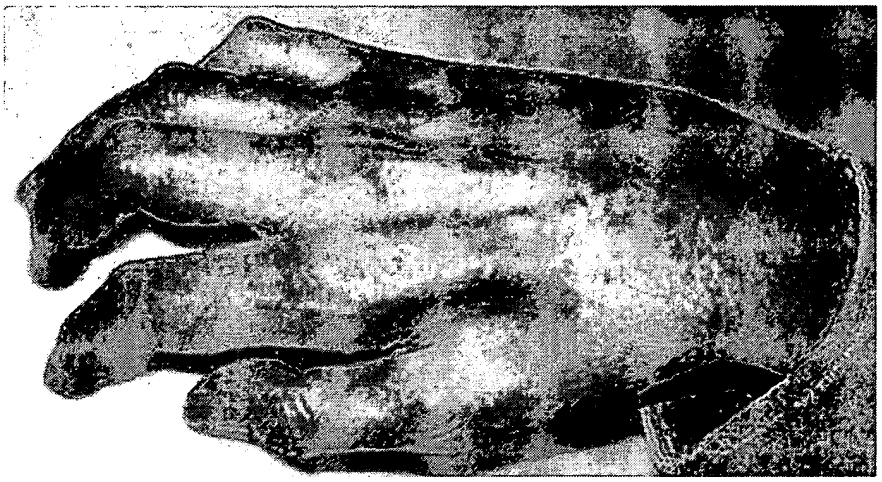
- Metabolic changes (Low CG syndrome)
  - Low plasma cystine & glutamine
  - High plasma glutamate
  - Low intracellular glutathione
  - High urea production
- Weight loss
  - Selectively in skeletal muscle
  - Not prevented by aggressive nutrition
- Natural killer cell function: Reduced
- Syndromes with low plasma cystine & glutamine levels
  - HIV: Late asymptomatic stage
  - Sepsis & trauma
  - Bowel disease: Crohn's; Ulcerative colitis
  - Chronic fatigue syndrome
  - Overtraining
- Changes may be reversed by N-acetyl-cystine (NAC) treatment
- Differs from starvation which has

- Low urea production
- Weight loss in most organs



Congenital myopathy

- Severe **wasting** involves the distal arms & legs.
- The most distal regions, the hands & feet, are relatively spared



Chronic denervation: Severe

- Severe **wasting** involves the distal arms & legs including the most distal regions, the hands & feet.
- Note atrophy of median (thenar) and ulnar innervated muscles in the hands.
- Severe trophic skin changes are present on the legs.

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2/9/2001

Stedman's Medical Dictionary 27th Edition

wasting (wast'ing)

1. SYN: emaciation. **2.** Denoting a disease characterized by emaciation.
salt ***w.*** inappropriately large renal excretion of salt despite the apparent need of the body to retain it.

MYOPATHY, NEUROMUSCULAR JUNCTION & NERVE DISORDERS: Points in differential diagnosis

1. Distinctive Features: Most myopathies have weakness that is maximal proximally.

Extraocular muscles weak
Myasthenia Gravis (MG)
Thyroid; Botulism
Mitochondrial: KS; PEO; MNGIE
Centronuclear; Multicore
Oculopharyngeal MD; IBM + Contracture
Oculopharyngodistal myopathy
Congenital ophthalmoplegias

Periocular without EOM Weakness
Dystrophies: Myotonic; FSH; Oculopharyngeal
Myasthenia Gravis (MG)
Congenital Myopathies
Polymyositis
Rule out: VII nerve lesion

Bulbar dysfunction
MG; Thyroid; Cranial nerve Δ
Oculopharyngeal MD
Distal myopathy (MPD2)
Polymyositis: IBM; Scleroderma
Motor neuron Δ: ALS
Pseudobulbar palsy; Fazio-Londe
Brown-Vialetto-van Laere; BSMA

Posterior neck weak
Common: MG; PM; ALS
Focal myopathy: Neck; Paraspinous
Rare: FSH dyst; LMN synd; IBM; Rod; PROMM; Acid maltase; ↓ K^+
Carnitine; Endocrine; Desmin

Distal & Proximal weakness
Dystrophy: Myotonic; FSH Scapuloperoneal
Myopathy: Congenital; Distal
Glygogenoses: Debrancher Phosphorylase b kinase
Neuropathy + Myopathy: Paraneoplastic; Sarcoid; Mitochondria; HIV;
Drugs (Amiodarone; Doxorubicin Colchicine; Chloroquine)

Acute weakness
Myasthenia gravis; Myoglobinuria
Myosin loss myopathy; Carnitine ↓
Periodic paralysis: X-Episodic Xp22
Hypo K^+: CACNA1S; SCN4A; KCNE3
Hyper K^+: SCN4A; KCNE3
Andersen: KCNJ2
Electrolyte disorders: K^+ ↑ or ↓; Mg ↑; PO_4 ↓; Barium
Rule out: Neuropathy; Spinal cord

Wasting > Weakness
Pathology: Type II atrophy
Cachexia: Wt loss > 15%
Disuse; Steroid myopathy;
Paraneoplastic; Aging

Weakness > Wasting
Polymyositis; Myoglobinuria;
Periodic Paralysis;
Myasthenia gravis;
Neuropathy with conduction block

Proximal arms weak
Dystrophy: Scapuloperoneal; FSH
Absent muscles; Shoulder joint Δ
MG; Neuropathic: ALS; P-LMN; Brachial plexopathy

Quadriceps weak
Myopathy: Becker; Ring fiber
Myositis: IBM; Mitochon; Focal
Nerve: Femoral; LS plexopathy; Diabetic amyotrophy; L3-L4 root

Myoglobinuria
Hereditary: Glycogenolysis; CPT II; Malignant Hyperthermia; Central core
King-Denborough; DMD (Some)
↓ K^+: Licorice: Li; Thiazide: Amphotericin; Laxative
Infections; Mitochondrial; Trauma
Muscle: Ischemia; Overactivity; PM
Neuroleptic malignant syndrome
Drugs: Heroin: Phencylidine; ε-ACA
Clofibrate + Renal failure;
Cyclosporine A + Lovastatin
Toxins: Venoms; IV drugs
Oral: Haff; Mushrooms; EtOH

Muscle activity
Brody's syndrome: ATP2A1
Cramps: Benign
Myoedema
Myotonia Congenita
Dominant (Thomsen): CLCN1 (Cl^-)
Recessive (Becker): CLCN1
Acetazolamide responsive: SCNA4
Myotonic Dystrophy 1: DMPK, CTG rep
Myotonic Dystrophy 2: ZNF9, CCTG rep
Paramyotonia: Na^+ channel (SCNA4)
Periodic paralysis, Hyperkalemic
Schwartz-Jampel: Perlecan
Neural & Spinal activity

Cardiac disorders
Dystrophy: DMD/Becker; Myotonic; McLeod; Emery-Dreifuss; Barth; Scapuloperoneal; Desmin
Polymyositis; Nemaline rod
Acid Maltase; Debrancher
Carnitine ↓; Desmin ↑
Mitochondrial; Amyloid
Drugs: Metronidazole; Emetine; Chloroquine; Clofibrate; Colchicine
Cardiomyopathy + cores
Periodic paralyses

Respiratory Failure
Myasthenia gravis
Myosin-loss myopathy
Acid Maltase
Amyloid; Desmin
Polymyositis (Jo-1)
Congenital Myopathy: Rod; Centronuclear
Hydroxychloroquine
Neural: Phrenic lesions
Arnold-Chiari; Churg-Strauss
Brachial plexopathy; ALS

GI disorders: See Neuropathy

Muscle pain
Myositis: + Connective tissue dis
Polymyalgia; Rhabdomyolysis
Infections: Trichinosis; Brucellosis
Myoadenylate deaminase ↓ (< 2%)
Myopathy +: Tubular aggregates; Focal ↓ mitochondria
Drugs: Azathioprine; Steroid ↓...
Rule out:
Small fiber neuropathy; Phlebitis
Bone & joint pain; Muscle Ischemia

Large muscles
Overusage: Myotonia; Exercise Neural Overactivity
Partial denervation
Endocrine: ↓ Thyroid; Acromegaly
Dystrophy: DMD; LGMD; Lipo
Infections: Cysticercosis; Trichinosis; Schistosomiasis
Drugs: β_2 adrenergic; Androgen
Storage: Glycogen; Amyloid Fat; Gangliosides
Short stature: Schwartz-Jampel; Myhre

Cramps
Normal: Single Muscles Post-contraction; Sleep
Electrolyte: Dehydration ↓ Na, Mg, Ca, Glucose
Thyroid; ↓ Adrenal
Drugs; Pregnancy; Spinal stenosis
Cramp-fasciculation; Familial
Myopathy: Becker
Motor neuron: ALS
Elecrically silent: phosphorylase Rippling muscle; Brody's

Contractures
Arthrogryposis
Bethlem Myopathy
Congenital MD
Dermatomyositis
Dystrophinopathies
Emery-Dreifuss
IM drug injections
Rigid spine syndrome
SMA: 5q; X-linked
Tel Hashomer
Williams-Beuren

CNS + Myopathy
Congenital MD: Santavuori (POMGnT1; 1p32); Merosin (6q22); Fukuyama (Fukutin; 9q31) Integrin-α7 (12q13)
Dystrophy: DMD; McLeod Myotonic; PROMM; HIBM (9p13)
Metabolic: Thyroid; Mitochondrial
Acid Maltase: Aneurysms
Phosphoglycerate Kinase
Myosin-loss
Necrotizing Encephalopathy; Pipestem capillaries
Hearing loss: FSH; Scapuloperoneal

Antibodies + Myopathy
MG: Anti-AChR Binding & Modulating
MG + Thymoma: Anti-striational vs. Titin; Actinin; Ryanodine R
LEMS: P-type Ca^{++} channel
Polymyositis:
t-RNA synthetase (Jo-1): Lung; Raynaud's; Arthritis
Signal recognition Particle: Acute
Mi-2: Dermatomyositis; Nail Δ
PM-Scl: PM + Scleroderma
Decorin: M-protein; Myopathy

CK: High > 1,000
Dystrophy
X-linked: DMD/Becker
Recessive: 2A-2I
Dominant: 1C; Ankle contractures
Distal myopathy: Miyoshi
Polymyositis
Acid maltase
Acute damage: Injection Rhabdomyolysis; Trauma
Thyroid: Hypo-

Inflammatory myopathies
Antibodies: Decorin; SRP; Mi-2; t-RNA synthetase (Jo-1 75%)
Dermatomyositis: Mi-2 Ab; Adult vs Child
Microvasculopathies: DM; SRP
Granulomatous ± Sarcoid
Idiopathic myositis: Poly-; Focal
Inclusion body (IBM); Infectious
Mitochondrial Δ in muscle
Systemic disease: Drugs; Collagen vascular; GVHD; Malignancy; Toxic
Hereditary: IBM; FSH

2. Myasthenic Syndromes

Acquired MG: Immune ± Thyroid or Thymoma; Childhood; Drug-induced; Neonatal Transient
Lambert-Eaton myasthenic syndrome (LEMS)
Congenital & Familial:
Presynaptic: Familial infantile (ChAT; 10q11)
↓ Synaptic vesicles & Quantal release
Congenital Lambert-Eaton-like
Episodic ataxia 2: CACNA1A; 19p13
Synaptic: AChE deficiency (ColQ; 3p25)
Postsynaptic: AChR α β δ ε; Rapsyn; Plectin
AChRs: Kinetic Δ & ↓ # @ NMJs
Slow AChR channel; ↓ Channel open time
AChRs: Kinetic Δ & Normal # @ NMJs
↕ Conductance & Fast closure of AChRs
↓ ACh-affinity & Fast-channel
AChRs: ↓ #s @ NMJs & Kinetic WNL
Rapsyn (11p11): ↓ AChRs @ NMJs
Plectin (8q24)
Apnea & Bulbar: SCN4A (17q35)
Other syndromes: Familial limb-girdle; Benign congenital MG & Facial malform
Congenital LEMS-like; Familial immune

3. Hereditary Myopathy Syndromes

Dystrophies: Limb-Girdle & Other
Dominant: 1A Myotilin (TTID), 5q31; 1B LMNA, 1q11; 1C Cav-3, 3p25; 1D 7q; 1E 6q23; 1F 7q32; 1G 4p21; Cytoplasmic body 2q24 & 2q21; Emery-Dreifuss LMNA; DM1 DMPK CTG rpt, 19q13; DM2 ZNF9, 3q21 Bethlem COL6A, 21q22 & 2q37; FSH 4q35; IBM3 Myosin HC2, 17p13; ZASP, 10q22; Oculopharyngeal PABP2 GCG rpt, 14q11; Spheroid body Desmin 2q35; αB-crystallin 11q22; Paget VCP, 9p13 *Dysplasia* Diaphys TGFB1, 19q13; Epiphys COL9A3, 20q13
Recessive: 2A Calpain-3, 15q15; 2B Dysferlin, 2p12; *Sarcoglycan* 2C γ, 13q12; 2D α, 17q21; 2E β, 4q12; 2F δ, 5q33 2G Telethonin, 17q11; 2H TRIM32, 9q31; 2I FKRP, 19q13; 2J Titin, 2q31; 4; Cav-3; CMD: NI CNS FKRP, 19q13; Rigid spine SEPN1, 1p35 Respiratory failure 1q42; Ullrich COL6A; 21q22 & 2q37
X-linked: Barth Tafazzin, Xp28; Autophagy Xq28; Emery-Dreifuss Emerin, Xq28; McLeod XK, Xp21 Becker & Duchenne Dystrophin; Xq21; Danon LAMP-2; Xq24; Scapuloperoneal

Distal Myopathies
Dominant:
Welander 2p13: Late; Hands & Ant. Legs
Finnish & Markesbery Titin, 2q31: Late; Ant Tib
Gowers-Laing (MPD1) MYH7, 14q11: Adult; Ant leg
Dystrophy + Rimmed vacuoles 19p13
IBM1: Quad weakness
MPD3: Adult, Asymmetric; LGD 1C
IBM +: Paget's VCP, 9p13; Resp failure 6q27
Oculopharyngodistal
Vocal cord & Pharyngeal (MPD2) 5q31
Myofibrillar: Desmin; αB-crystallin; TTID; ZASP
Recessive:
Nonaka & IBM2 GNE, 9p12: Quad sparing
Miyoshi & LGD 2B Dysferlin, 2p12-14 Early adult; Posterior leg
LGD 2G Telethonin, 17q11: Teens; Ant leg & Prox

Other myopathies
Barnes; Congenital; Lipid; Glycogen;
Familial MG; Tubular Aggregates

Alan Pestronk 1/24/2005: More information at Neuromuscular Website: http://www.neuro.wustl.edu/neuromuscular/